Predictive value of ischemia modified albumin in determining the severity of coronary artery disease

Eurasian Clinical and Analytical Medicine Original Research

Ischemia modified albumin in coronary artery disease

Oguzhan Toklu[1], Sedat Abusoglu[2], Fusun Ustuner[3], Murat Yesil[1], Evren Akgol[4]

[1] Department of Cardiology, İzmir Ataturk Training and Education Hospital, İzmir, Türkiye.

[2] Department of Biochemistry, Faculty of Medicine, Selcuk University, Konya, Türkiye.

[3] Department of Biochemistry, İzmir Ataturk Training and Education Hospital, İzmir, Türkiye.

[4] Biochemistry Clinic, Birecik State Hospital, Şanlıurfa, Türkiye.

Abstract

Aim: Diagnosing myocardial ischemia in patients with chest pain via non-diagnostic electrocardiograms (ECG) and cardiac markers is challenging. The objective of this study is to determine the predictive value of Ischemia Modified Albumin (IMA) levels for coronary artery disease (CAD) severity in Unstable Angina Pectoris (USAP) patients.

Methods: One hundred and twenty-five patients with chest pain and non-diagnostic ECG findings were included in the study. All patients underwent coronary angiography and CAD severity was evaluated by the Gensini scoring system. Patients were divided into two groups. IMA levels were measured by spectrophotometry.

Results: Mean IMA levels were significantly higher in patients than in healthy persons (0.762±0.059; 0.681±0.055 ABSU respectively; p<0.001). In the ROC analysis the cut off value of 0.718 demonstrated CAD with a sensitivity of 76% and specificity of 74%. Positive correlation was found between IMA levels and Gensini score (p<0.001).

Conclusion: IMA is a strong predictor of CAD in patients with unstable angina pectoris and is positively correlated with the severity of the disease.

Keywords

ischemia modified albumin (IMA), unstable angina pectoris (USAP), gensini score, coronary artery disease

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Corresponding Author: Evren Akgol, Biochemistry Clinic, Birecik State Hospital, Şanlıurfa, Türkiye.

P.: +90 505 765 67 75 · **E-Mail:** akgolevren@yahoo.com

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Introduction

Cardiovascular diseases are leading causes of death in industrialized countries in modern days and it is expected this will also be the case in developing countries by 2020.[1] Among these, coronary artery disease (CAD), associated with high mortality and morbidity, is the most commonly occurring form of cardiovascular disease. Silent ischemia, stable angina pectoris, unstable angina pectoris, myocardial infarction (MI), congestive heart failure, and sudden death are among the presenting clinical features of ischemic heart disease. Patients with angina pectoris constitute most of the acute hospitalization cases in Europe.Acute coronary syndrome (ACS) is just such an emergency situation that requires early diagnosis and treatment. Recent studies indicate that patients with ACS apply to the emergency services with non-specific symptoms such as dyspnea, sweating, nausea-vomiting, and malaise other than pain. Additionally, the fact that pain in 33% of patients and the ECG findings in 40% of patients are not diagnostic has further increased the importance of biochemical parameters in the diagnosis of ACS.[2,3] In recent years, identification of the development of structural changes in serum albumin in ischemic conditions has allowed for the discovery of a new serum cardiac ischemic marker. The last amino-terminal in albumin structure is the region of the binding of transition metals, such as cobalt, copper, and nickel.[4] The albumin that has had these structural changes is called, "ischemia modified albumin" (IMA) and the changes in the albumin molecule can be colorimetrically measured by adding some cobalt to the patient's serum. High IMA values are seen in end-stage renal failure, intestinal ischemia, and cere-brovascular ischemia.[5,6] It is suggested that the increase in IMA concentration can be used as an early marker of myocardial ischemia in evaluation of patients with ACS.[7,8] The aim of this study was to investigate the predictive value of the level of IMA, a new and early ischemic marker in patients with unstable angina pectoris, in determining the prevalence and severity of coronary artery disease assessed with Gensini score by coronary angiography.

Materials and Methods

Study Patients and Protocol

This study was approved by the ethics committee of Izmir Atatürk Training and Research Hospital on 29.01.2009 (approval number: 533). 125 patients were hospitalized in the Cardiology Clinic for coronary angiography, with normal troponin levels during follow-up and no changes in serial ECG during follow-up. They were also diagnosed with USAP according to the criteria of the European Cardiology Society and the American Association of Cardiology (ESC/ACC). Of the patients who applied to the emergency service of Izmir Atatürk Training and Research Hospital with symptoms of chest pain suggestive of acute myocardial ischemia (pain continuing for more than 20 minutes, squeezing or burning in nature, and localized in the precordial, retrosternal, or epigastric regions, or spreading to the left arm or the jaw), were included in the study. Blood samples of 8 mL each were drawn from the patients who pre¬sented to the emergency department with chest pain. The blood was drawn intopure gel tubes that were centrifuged at 4000 cycles/min for 5 minutes after waiting 30 minutes for clot formation. After routine measurements of cTnI and bio¬chemical measurements, serum samples were stored at –20 °C for later IMA and albumin measurements.Pregnant patients, those with a previous or recent history of cerebrovascular events, peripheral vascular disease, renal failure, acute abdomen, a history of MI and revascularization (coronary by-pass, percutaneous intervention), increased cardiac enzyme levels and positive ECG findings during follow-up, diagnosis of valvular heart disease in routine ECG, ventricular ejection fraction lower than normal, serum albumin level < 3 g/dL and > 5.5 g/dL, and those younger than 18 years old were not included the study.

ECG Data

A standard 12 lead ECG (with a speed of 25 mm/sec, amplitude of 10 mm/mV) was taken from the patients who applied to the emergency service with symptoms of chest pain.

Biochemical Tests

Cardiac Troponin I (cTnI) measurements were completed by using direct chemiluminometric technology in an Siemens ADVIA Centaur CP autoanalyzer. The patients who did not have an increase in troponin levels during the follow-up were included the study. The albumin measurements were taken using the bromocresol green method with an Architect C16000 (Abbott Diagnostic, USA) autoanalyzer. IMA measurements were completed with the albumin cobalt-binding test defined by Bar-Or, et al.[4] This test depends on the colorimetric measurement of the colored complex that is formed by cobalt, added to the sample and does not bind to albumin, with the dithiothreitol. The results were given as Absorbance Units (ABSU). In summary, blood was collected for the IMA measurements in test tubes that had the serum separated. Specimens were frozen at –20 °C or colder within two hours. Frozen samples were gently vortexed after thawing.

Coronary Angiography

Selective coronary angiography was completed with a Judkins catheter by femoral approach (Philips H 3000 POLYC-OMCP, 30 square/sec, 6-7 F guide catheter). LAD and Cx were evaluated at a minimum of four positions (left cranial, right cranial, right caudal, left caudal) and RCA was evaluated at a minimum of positions (60° left, 60° right). The coronary reference segment was selected from the proximal and distal parts of the lesion. The diameter and the narrowness of the lumen were measured through calibration of the guide catheter. The narrowing of the coronary lumen was evaluated by three cardiologists who were unaware of the clinical condition of the patient. The stenosis of the vascular lumen of about 70% or more was accepted as critical coronary stenosis. The coronary angiographies were interpreted by the coronary artery disease severity score, the previously defined Gensini score. The coronary arterial tree was investigated in a segmental fashion. According to the functional importance, the multiplication factor was 5 and 0.5 for the main coronary artery and the distal segments, respectively, and it was multiplied with the luminal diameter scores (0, 1, 2, 4, 8, 16, and 32). At the end a total Gensini score reflecting the severity of the coronary artery disease was obtained as a numerical value.

Echocardiography

Routine echocardiography was carried out on the patients hospitalized for coronary angiography in the standard view of the parasternal long axis, parasternal short axis, apical four chamber, and apical five chamber positions using a General Electric Vivid 3 Version 2.3. Patients with normal left ventricular systolic function, wall motion indices, and valvular functions were included in the study.

Statistics

The calculations and statistical analyses were calculated using the SPSS 15.0 statistical program. The continuous variables were given as mean± standard deviation in a confidence interval of 95%. The difference between the groups was evaluated with student's t-test, the frequency of the categorical variables was given, chi-square test was used for continuous variables, and a value of $p<0.05$ was accepted as statistically significant. The ROC curve was used to determine the sensitivity and specificity of IMA. The relationship between IMA and Gensini scores was evaluated with Pearson's correlation test.

Results

There was no significant difference between the mean age of the

males and the females in Group 1 (60.67±9.94, 59.68±8.87, respectively, p=0.053) and in Group 2 (56.92±0.82, 60.71±4.78, respectively, p=0.486).

The diffuseness and the severity of the disease in 75 patients who had coronary artery disease and critical coronary artery stenosis in at least one coronary artery according to the coronary angiography were scored by Gensini score and designated as Group 1. 50 patients with normal coronary arteries or noncritical coronary artery disease were designated as Group 2. Demographic data of the patients participating in the study is presented in Table 1.

While there was no significant difference between Group 1 and 2 in terms of the albumin levels of the patients (p=0.950), the IMA levels of the patients in Group 1 was significantly higher than in Group 2 (Figure 1) (p<0.001). The patients who participated in the study were using various drug therapies at the time of the application and there was no diagnosis of coronary artery disease in any of these patients (Table 2).

There was no significant gender difference in IMA, albumin levels, or Gensini scores in Group 1, according to the gender-based analysis (Table 3). There was a positive correlation between Gensini scores and IMA levels in patients in Group 1 according to the Pearson's correlation analysis and it was statistically significant (p<0.001) (Figure 2). According to the analysis of the ROC curve, IMA is a highly diagnostic test (area under curve (AUC) = 0.852, p<0.001) and the IMA levels of about 0.685 ABSU is diagnostic with a sensitivity of 96% and specificity of 64% (Figure 3). It was found that for use, the positive predictive value was 80 when the positive likelihood ratio was 2.67 and the negative likelihood ratio was 0.06 and the positive predictive value was 91.4. It was found that the relationship between the gender and IMA was not statistically significant in either group (p=0.759 for Group 1, p=0.689 for Group 2).

Table 1. Demografic data of patients

	Group 1 (n=75)	Group 2 (n=50)	P value
Gender			
Male (%)	40 (53)	26 (52)	0.973
Female (%)	35 (47)	24 (48)	0.988
Diabetes Mellitus (%)	11 (14.7)	10 (20)	0.471
Hypertension (%)	42 (56)	22 (44)	0.465
Smoking (%)	41 (54.7)	24 (48)	0.472
Hyperlipidemia (%)	41 (54.7)	24 (48)	0.472
Age			
Male (Mean±SD)	60.67±9.94	56.92±0.82	0.053
Female (Mean±SD)	59.68±8.87	60.71±4.78	0.486

Table 2. Drug medications of groups

Drug	Group 1 (n=75)		Group 2 (n=50)		P value
	n	%	n	%	
Amlodipine	14	14.6	5	10	0.069
Acetylsalicylic acid	61	81.3	35	70	0.083
Atenolol	4	5.3	3	6	0.678
Benidipine	2	2.6	1	2	0.481
Gliclazide	1	1.3	2	4	0.057
Indapamide	8	10.6	4	8	0.183
Lisinopril	9	12	4	8	0.219
Metformin	8	10.6	6	12	0.149
Metoprolol	7	9.3	5	10	0.597
Nifedipine	1	1.3	1	2	0.193
Perindopril	1	1.3	1	2	0.193
Pioglitazone	2	2.6	2	4	0.241
Zofenopril	1	1.3	1	2	0.193
Hydrochlorothiazide	16	21.3	11	22	0.649

Table 3. Gensini Score, serum IMA, and albumin comparision between males and female patients

	Group 1 (n=75)		P value
	Male (n=40)	Female (n=35)	
IMA (ABSU)	0.748±0.053	0.776±0.061	0.849
Albumin (g/dL)	3.74±0.57	3.65±0.51	0.941
Gensini Score	41±0.5	39±0.5	0.648

Discussion

The primary issue that must be addressed in patients applying to emergency services with chest pain is acute coronary syndrome.[9] ECG and biochemical markers used for the diagnosis of ACS at the present time may be undiagnostic in approximately half of the patients at the time of application. This situation complicates the diagnostic period, prolongs the duration of hospitalization, and thus increases

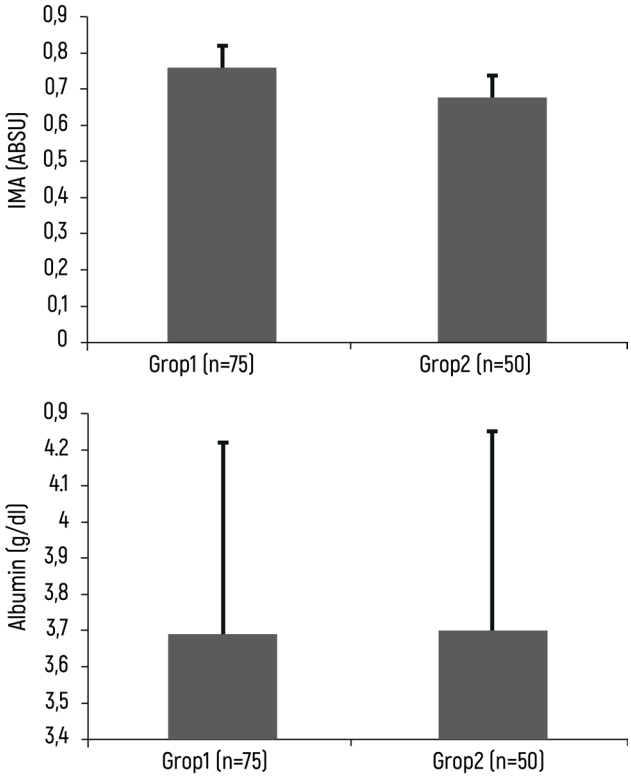

Figure 1. Comparision of serum IMA and albumin levels of patients and controls

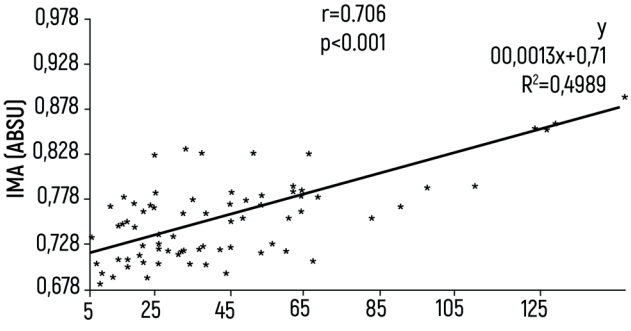

Figure 2. Correlation of Gensini score and serum IMA levels.

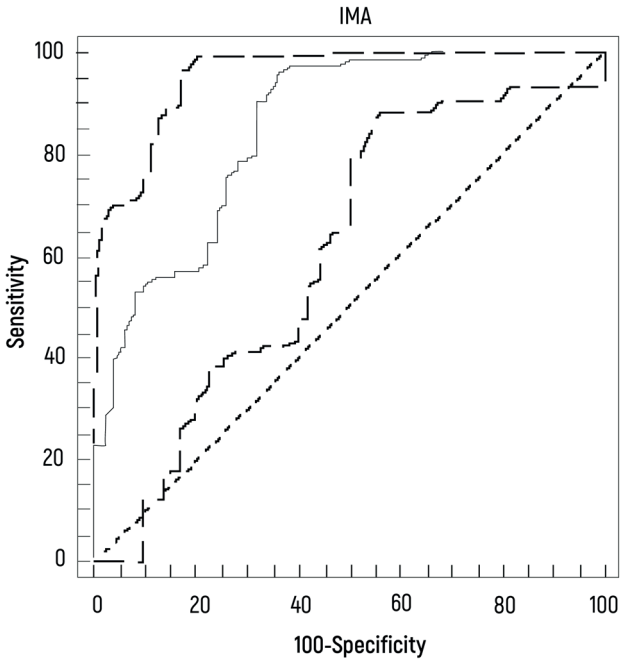

Figure 3. ROC curve for serum IMA.

the workload and hospitalization costs.[10,11] IMA is a newly identified biochemical marker, approved by FDA, that has been frequently touted in recent years in the demonstration of myocardial ischemia.[11] The studies suggest that IMA could be used as an early marker in patients having undiagnostic results by ECG and cardiac markers during the application to emergency services, and that it is an independent predictive factor for cardiovascular morbidity.[12-14]

In a study, it was found that in patients who had severe coronary artery lesions indicated by coronary angiography, following a positive exercise test, the IMA levels measured in blood samples taken immediately after the exercise were significantly higher and this further indicates the reliability of the exercise test.[15] In a study done by Anwaruddin, et al., the diagnostic value of the measurement of IMA in combination with other standard biomarkers (CKMB, myoglobin, cTnI) in patients who applied to emergency services with chest pain and suspicion of myocardial ischemia was investigated. As a result, the negative predictive value and sensitivity of measurement of IMA in combination with standard biomarkers in determination of ischemia were found as 92% and 97%, respectively, and IMA's use in standard analysis was recommended.[16]

In a meta-analysis investigating therole of IMA in the exclusion of acute coronary syndrome in emergency services, it was stated that the determination of negative troponin and negative IMA levels in combination with non-diagnostic ECG in patients presenting with chest pain has a high predictive value.[17]

In some studies, IMA levels were compared in the blood samples taken before and after elective percutaneous transluminal coronary angioplasty (PTCA). It was shown that the IMA levels measured after the procedure were significantly higher than the levels measured before the procedure, and these high levels are significantly correlated with coronary collateral circulation, duration, count, pressure of balloon in flation, and chest pain and ECG changes produced during the procedure.[18-20] In our study, it was found that in patients who applied to emergency services with chest pain and normal cTnI enzyme levels, without any pathological changes in serial ECG follow-up and with normal left ventricular systolic dysfunction, normal wall motion indices, and without any valvular disease in echocardiography, and who were hospitalized with the diagnosis of USAP, the basal IMA levels were significantly higher in the group that had diffuse coronary artery disease according to the angiography findings when compared with the group that had no severe coronary artery disease. Furthermore, it was demonstrated that in patients with coronary angiography and the diagnosis of USAP, the IMA levels were a powerful predictor in the determination of the diffuseness and severity of coronary artery disease determined by Gensini score. The significant positive correlation between IMA levels and Gensini score calculated according to coronary angiography showed that as the diffuseness and severity of the coronary artery disease increases, the IMA levels also increase, parallel to this increase. This shows that increased IMA levels might be helpful in diagnosing USAP. It is reported that for the albumin amount in the samples in which IMA measurements were completed, the reference levels do not produce a significant difference in IMA levels.[21] However in one study it was reported that IMA levels only change according to albumin levels.[22] Because of this, it is recommended that correcting IMA levels according to albumin levels would be beneficial.[23] In our study there was no difference in albumin levels between the control and the case groups. Therefore, it was thought that the high IMA levels in Group 1 are independent of the albumin levels.

Diabetes mellitus, hypertension, and smoking are important risk factors for CAD. It was reported in the literature that IMA levels are higher in diabetic patients when compared to healthy individuals.[24] In our study, it was demonstrated that there was no significant difference in IMA levels between the individuals who had risk factors for CAD, such as associated diseases or smoking, and the individuals without these risk factors. Furthermore, there is no significant relationship between IMA levels and age, another risk factor for CAD.

One of the important limitations of our study was the variation of the frequency and duration of chest pain in patients who applied to emer gency services and who were involved in our study. Although it is determined that IMA levels return to normal values within three hours after PTCA practices, which is an in-vivo model of myocardial ischemia, the ischemia formed in these models is transient and the ischemic process terminates at the end of PTCA.[19] As the chest pain occurring in USAP is thought to be due to myocardial ischemia, one can infer that the ischemic process continues and as a result, the IMA formation also continues in patients who applied to emergency services with chest pain. This could be investigated in large-scale studies in which the frequency and the duration are standardized equally.

There is limited knowledge about the interactions of IMA, as it is a new biomarker. We believe that the investigation of IMA levels in events that cause the formation of reactive oxygen radicals that have an effect on the development of IMA would be useful in the determination of the interactions of this marker.

Conclusion

In our study it was demonstrated that high levels of IMA, a newly used biochemical marker, independent of associated risk factors, has a strong predictive value in determination of coronary artery disease in patients that applied to emergency services with the symptoms of chest pain. It was also shown that these values increased parallel to the diffuseness and the severity of the disease according to the angiography findings.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed Consent

Informed consent was obtained from all participants.

Conflict of Interest

The authors declare no conflicts of interest.

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None.

Scientific Responsibility Statement

The authors declare that they are responsible for the scientific content of the article, including the study design, data collection, analysis and interpretation, manuscript preparation, and approval of the final version of the manuscript.

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